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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/614,003	07/11/2000	Walter Gehring	7326-092	1043

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PENNIE AND EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 100362711

EXAMINER
KATCHEVES, KONSTANTINA T

ART UNIT	PAPER NUMBER
1636	8

DATE MAILED: ~~03/11/2002~~

RE STANDARD
4/3/02

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/614,003	Applicant(s) GEHRING ET AL.	
	Examiner Konstantina Katcheves	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,16-18 and 22-83* is/are pending in the application.

4a) Of the above claim(s) *6,11,12,16,17,22,23,35-49,53-62,67 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10,18,24-34,50-52,63-66 and 69-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-12, 16-18 and 22-83 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group IV in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the examination of at least claims 1-5, 7-10, 13-15, 18-21, 24-34, 50-52, 63-66 and 69 would not present an undue search burden. This request is found persuasive and accomodated. Accordingly, claims 1-5, 7-10, 13-15, 18-21, 24-34, 50-52, 63-66, 69-83 have been examined. The requirement is otherwise still deemed proper and is therefore made FINAL.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-10, 13-15, 18-21, 24-34, 50-52, 63-66, 69-83 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-102 of copending Application Serial No. 09/113399 (hereinafter '399 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are an obvious variation of the claims of the '399 application.

The instant claims are broadly drawn to a method for altering cell fate comprising altering Notch pathway function in the cell by contacting the cell with a modulator of Notch pathway function. Said modulator also alters the function of a gene pathway that is not Notch. The claims of the '399 application are drawn to a method for the modulation of a signal transduction pathway by modulating Notch function (*i.e.* Notch pathway) with an agonist such that a signal transduction pathway that is not Notch is affected. One of ordinary skill in the art would have recognized that the method involved in the alteration of cell fate in the instant application and the method for modulating a signal transduction pathway in the '399 application are the same. Therefore, the instant invention would have been obvious to one of ordinary skill in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

Claims 1-5, 7-10, 13-15, 18-21, 24-34, 50-52, 63-66, 69-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The instant claims are broadly drawn to a method for altering cell fate comprising altering Notch pathway function in the cell by contacting the cell with a modulator of Notch pathway function. Said modulator also alters the function of a gene pathway that is not Notch. Given their broadest reasonable interpretation, the instant claims are drawn to a method that encompasses many signaling pathways, modulators of Notch and cells from different organisms. The antagonists of Notch include diverse molecules and mechanisms of action such as antisense nucleic acids against Notch itself or against Suppressor of Hairless or Deltex. Antagonist include antibodies against Notch, fragments of Notch regulators, Delta or Serrate, or cells expression non-functional Delta or Serrate ligands. Thus, the already complex invention of altering cell fate in greatly exacerbated by the extreme breadth of the claims which encompass a large number of different cell types having different developmental fates and a large number of different potential Notch antagonists which are chemically, structurally, biologically and functionally different from one another.

The modulation of cell fate by altering Notch pathway functions is unpredictable with regard to achieving specificity in the inhibition of a signal transduction pathway because the art is poorly developed. The breadth of the instant claims presumes that Notch modulators work uniformly or efficiently across a broad spectrum of cells, and moreover, that the biochemical activities of Notch proteins function identically from cell type to cell type. Blaumueller et al. (Cell Vol.90 1997) recognize that:

> The question of what particular roles are played by the assorment of paralogs within the Notch suprefamily, in combination with the various paralogs of the other pathway components, remains unclear. See page 287, column 1.

Moreover, the authors indicate that questions also remain regarding the biochemistry of the Notch pathway. Fleming et al. (Trends Cell Biology vol.7 1997) teaches that: "There is much we still do not understand regarding the interaction between NOTCH and its ligands, especially how they influence the expression and therefore the activity of Notch pathway elements." See page 440, third paragraph).

Another factor to consider is the guidance and working examples provided in the specification. The specification fails to adequately supplement the failings of the art. First, the specification does not teach how to specifically modulate Notch or any signal transduction pathway. The specification fails to show examples or teachings that would enable one of skill in the art to reliably practice the method in systems other than Drosophila. The specification provides no working examples of the claimed invention, and the working examples provided are limited to Drosophila cell systems.

In summary, the complexity of the instant invention would not enable one of skill in the art to make and use the invention due to: (1) the complex nature of the invention requiring the manipulation of Notch and other signal pathways to alter an already established cell fate; (2) the breadth of the claims which encompass any differentiated cells; (3) the breadth of the claims which encompass the use of any potential agonist or antagonist of Notch pathway activity; (4) the lack of significant guidance from the specification as to how to practice the claimed invention or mechanistic explanation as to how the Notch pathway functions in differentiated cells; (5) the lack of significant guidance and relevant working examples in the specification as to how to practice the claimed invention or explanation of the mechanism of how the Notch pathway functions in mature cells and interacts with other pathways; and (6) the underdeveloped

and unpredictable state of the of the art regarding manipulating cell fate by manipulating Notch pathway function along with the function of other pathways *in vitro* or *in vivo*. For the foregoing reasons, an undue amount of experimentation would be required of one of skill in the art in order to practice the invention claimed.

Claims 1-5, 7-10, 13-15, 18-21, 24-34, 50-52, 63-66, 69-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods, does not reasonably provide enablement for *in vivo* methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's invention of the instant claims is drawn to a method for altering cell fate comprising altering Notch pathway function in the cell by contacting the cell with a modulator of Notch pathway function. Said modulator also alters the function of a gene pathway that is not Notch. Given their broadest reasonable interpretation, the instant claims are drawn to a method that encompasses many signaling pathways, modulators of Notch and cells from different organisms. The instant invention broadly encompasses both *in vitro* and *in vivo* methods.

As discussed above, the instant invention is extremely complex and very unpredictable. This already complex invention is made more unpredictable because in encompasses poorly developed gene therapy methods.

Palu et al. (J. of Biotech. Vol.68 1999) discuss the inherent difficulties transfecting cells *in vivo* by targeted delivery mechanisms. Transferred genes can be induced to function in a whole animal; however, no approach has been fully successful for *in vivo* gene transfer. See

Palu page 10 and figure 1. Moreover, the main obstacle to the development of gene therapy is the targeted long-term expression of the transgene. The *in vivo* transfection of cells has not been fully successful for many reasons including the complexity the biological systems of living organisms, the inability of the genes to reach enough of the target cells, and the inability of the genes to function properly or for a significant period of time even if they do reach the cells. See Palu page 10.

The examples provided fail to show the practice of the invention wherein the vector is directly injected into a subject organism. Upon examination of Applicant's disclosure, no evidence or data is apparent that the vector will reasonably reach its target location, deliver the a the claimed antagonist to the target cell in an amount sufficient to inhibit cell growth or induce apoptosis in a human subject. Applicant's specification does not overcome the state of the art, thus the instant claims are not enabled for *in vivo* methods of transforming cells. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure. Upon examination of Applicant's disclosure, no evidence or data is apparent that the vector will reasonably reach its target location, deliver the antagonis to the target cell in an amount effective to alter cell fate as claimed. Considering the inherent difficulties in the art as described by Palu et al., Applicant's disclosure does not teach how to overcome those obstacles. Moreover, the specification also does not clearly set forth a purpose for altering "cell fate" *in vivo.* For the foregoing reasons and absent evidence to the contrary, the instant claims are not enabled for altering cell fate *in vivo*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-10, 13-15, 18-21, 24-34, 50-52, 63-66, 69-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. First, there is no terminal or final step that creates a nexus between step (c) of subjecting the cell to particular conditions and the preamble, which claims a method for altering cell fate. Second, claim 1 recites a method with three method steps, steps (a), (b), and (c). However, steps (a) and (b) recites method steps within each of these steps. The claim is inherently unclear because it recites method steps within method steps. The claim should be corrected to more precisely claim the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (703) 305-1999. The examiner can normally be reached on Monday through Friday 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3388.

Konstantina Katcheves
March 11, 2002

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600